Journal of Cardiology (2010) **55**, 391—396

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jjcc

Original article

Predictor of subsequent target lesion revascularization in patients with drug-eluting stent restenosis undergoing percutaneous coronary intervention

Yosuke Takasawa (MD)[a,b], Raisuke Iijima (MD, PhD)[a,*], Masanori Shiba (MD)[c], Masato Nakamura (MD, PhD, FJCC)[a], Kaoru Sugi (MD, PhD, FJCC)[a]

[a] *Division of Cardiovascular Medicine, Ohashi Medical Center, Toho University, 2-17-6 Ohashi Meguro-ku, 153-8515, Tokyo, Japan*
[b] *Division of Cardiovascular Medicine, Toshiba Hospital, Tokyo, Japan*
[c] *Division of Cardiovascular Medicine, Nissan Tamagawa Hospital, Tokyo, Japan*

Received 29 October 2009; received in revised form 14 December 2009; accepted 12 January 2010
Available online 7 February 2010

KEYWORDS
Drug-eluting stent;
In-stent restenosis;
Percutaneous coronary intervention

Summary
Background: The best way to treat in-stent restenosis (ISR) after drug-eluting stent (DES) implantation remains unclear. The aim of this study was to evaluate angiographic restenosis and target lesion revascularization (TLR) at 8 months after intervention in patients with DES-ISR, and to identify predictive factors of subsequent TLR after treatment of DES-ISR.
Methods and results: A total of 100 patients with 105 lesions underwent subsequent intervention for DES-ISR between April 2004 and January 2009. At baseline, focal and diffuse ISR were observed in 76.2% and 23.8%. DES-ISR was treated by five modalities: sirolimus-eluting stent ($n=42$); paclitaxel-eluting stent ($n=24$); balloon angioplasty ($n=23$); cutting balloon angioplasty ($n=14$); and bare-metal stent ($n=2$). Angiographic follow-up data were available for 95 lesions (91%). The rates of angiographic restenosis and TLR were 37.9% and 33.3%. Late loss of sirolimus-eluting stent, paclitaxel-eluting stent, cutting balloon, and balloon angioplasty were 0.50 mm, 0.49 mm, 0.93 mm, and 1.10 mm. By multivariate analysis, totally occluded ISR (OR 15.43, $p=0.0005$), diabetes mellitus (OR 3.45, $p=0.02$), and re-stenting with DES (OR 0.14, $p=0.0002$) were identified as independent predictors of TLR.
Conclusions: The restenosis rate was significant in this cohort of patients with DES-ISR. Angiographic pattern of DES-ISR and diabetes mellitus are the most important predictors of TLR, whereas re-stenting with DES is protective.

* Corresponding author. Tel.: +81 3 3468 1251; fax: +81 3 3468 1269.
E-mail address: raisuke@live.jp (R. Iijima).

0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2010.01.003

Introduction

In-stent restenosis (ISR), which is almost always attributable to intimal hyperplasia, was a significant clinical problem in the era of bare-metal stents (BMS) [1]. Several percutaneous coronary intervention (PCI) techniques using balloon angioplasty and atherectomy devices failed to improve the long-term outcomes after treatment of ISR [2—4]. Subsequently, an additional stent implantation with drug-eluting stent (DES) has emerged as the most promising way to treat BMS-ISR [5,6]. The advent of DES remarkably reduced intimal hyperplasia after stent implantation and has demonstrated in the pivotal trials that the rate of restenosis approximated to single digits in selected patients. Still, DES has not eliminated restenosis completely [7]. As expected, the rates of angiographic restenosis and target lesion revascularization (TLR) are increasing when the use of DES widened among patients with off-label indications and those with more complex lesions [8,9]. Therefore, even in the era of DES, ISR has become an important clinical issue. Previous studies have reported two approaches, a balloon angioplasty or a re-stenting with second DES, to treat for DES-ISR, but the optimal management for DES-ISR is still not clearly defined [10,11]. Identifying predictive factors for repeat DES-ISR may help improve outcomes after PCI in the DES era. The aim of this study was to evaluate angiographic restenosis and TLR at 8 months after PCI in patients with DES-ISR, and to identify predictive factors of subsequent TLR after treatment of DES-ISR.

Methods

Study population

This analysis comprised a total of 100 patients with 105 lesions undergoing intervention for DES-ISR from April 2004 to January 2009 from 3 hospitals. All lesions were previously implanted on de-novo lesions by either a sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson, Miami Lakes, FL, USA) or paclitaxel-eluting stents (Taxus; Boston Scientific, Boston, MA, USA). The eligible patients were: (1) first ISR, which was defined as luminal re-narrowing greater than 50% within the stented segment or within a 5 mm segment either proximal or distal to the stent edges; (2) objective evidence of ischemic signs, either symptoms or changes in ST-T segment on the resting electrocardiogram, or inducible ischemia with exercise stress test. Written informed consent was given by all patients participating in the study.

PCI and procedural management

A bolus of 100 IU/kg of heparin was administered after insertion of the sheath and titrated to maintain an activated clotting time >250 s throughout the procedure. The device to treat ISR was selected at operator discretion. The subsequent PCI was performed either with balloon angioplasty including cutting balloon angioplasty or with re-stenting by the same or a different DES. Target lesions were predilatated with conventional angioplasty balloons. After stent implantation, high-pressure balloon inflation was performed to achieve a satisfactory angiographic result of less than 25% residual stenosis by visual estimate. All patients received aspirin 100 mg plus ticlopidine 200 mg or clopidgrel 75 mg per day for at least 12 months and other cardiac medications prescribed by the physicians.

Follow-up and definitions

Angiographic follow-up was scheduled at 8 months after PCI for DES-ISR. TLR was defined as revascularization involving the target lesion. Based on the classification reported by Mehran et al., ISR was classified on the basis of length of the restenotic lesion in relation to the stent length, namely 3 types of ISR have been defined: (1) focal ISR $\leq$10 mm length; (2) diffuse ISR >10 mm, within the stent borders; (3) totally occluded ISR [12]. Stent fracture was defined as complete separation of the stent by angiographic estimate. Follow-up was achieved in all patients. Patients who had cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory evaluation.

Quantitative coronary angiography

Quantitative coronary angiography was performed before, immediately, and 8 months after the procedure according to edge detection algorithms. Minimal lumen diameter (MLD), reference vessel diameter, diameter of stenosis (DS), and lesion length were measured using a single matched worst view. Late luminal loss was defined as the difference between the MLD immediately after the procedure and the MLD at 8 months after PCI. The 2nd ISR (subsequently restenosis after treatment of DES-ISR) was defined as greater than 50% DS by quantitative coronary angiography on follow-up angiography.

Statistical analysis

The data are presented as mean $\pm$ SD or counts (%). Differences between groups were assessed using ANOVA test for continuous variables. For the main analysis to identity independent predictors of TLR, we used a 2-step analysis. (1) Univariate analysis was used to select the clinical, angiographic, or procedural factors of TLR. Continuous variables were transformed to binary data with 1 for the presence of assumed risk factor and 0 otherwise. For example, age was dichotomized to elderly or not ($\geq$65 years versus <65 years), ejection fraction dichotomized to low or normal (<40% versus $\geq$40%), and treatment for DES-ISR also dichotomized to the 2 strategies (re-stenting with DES [both sirolimus- and paclitaxel-eluting stents] versus balloon angioplasty [included cutting balloon angioplasty]). We also used the median of each factor as the cut-off point for this division, avoiding arbitrary divisions. (2) Univariate predictors with $p < 0.05$ were entered into a stepwise multivariate logistic regression model. The odds ratio (OR) and 95% confidence intervals (CI) were calculated for the final multivariate model. Statistical significance was accepted for all p-values < 0.05.

Table 1 Baseline characteristics of patients.

	$n = 100$ (%)
Age, years	66 ± 11
Women, *n*	16 (16)
Arterial hypertension, *n*	42 (42)
Diabetes mellitus, *n*	57 (57)
Hypercholesterolemia, *n*	52 (52)
Current smoking, *n*	65 (65)
Hemodialysis, *n*	23 (23)
Left ventricular ejection fraction, %	59 ± 15
Clinical presentation	
Stable angina, *n*	95 (95)
Acute coronary syndrome, *n*	5 (5)

Data are presented as number of patients and lesions (%) or mean ± SD.

Results

The baseline clinical and angiographic characteristics are shown in Tables 1 and 2. The mean age was 66 years, 16% of patients were women, 57% had diabetes, and 23% of patients were on hemodialysis. The most frequent clinical presentation pattern was stable angina when undergoing PCI for DES-ISR. A diffuse ISR was observed in 25 lesions (23.8%) and occlusive ISR pattern in 13 lesions. On the other hand, focal ISR pattern was seen in 80 lesions (76.2%). At the time of initial stent implantation, bifurcation stenting with 2 DES was placed in 28 lesions and the mean stent length was 43 mm. ISR after sirolimus- and paclitaxel-eluting stents was seen in 88 (83.8%) and 17 (16.2%) lesions, respectively. DES-ISR was treated by five modalities, including sirolimus-eluting stent, paclitaxel-eluting stent, balloon angioplasty, cutting balloon angioplasty, and BMS (Table 3). When looked at by type of DES-ISR, ISR after sirolimus-eluting stent was treated by the following devices: sirolimus-eluting stent implantation (43.2%); paclitaxel-eluting stent implantation (14.8%); balloon angioplasty (25%); cutting balloon angioplasty (14.8%); and BMS implantation (2.2%). Whereas treatment of ISR after paclitaxel-eluting stent was used, included paclitaxel-eluting stent implantation (64.7%), sirolimus-eluting stent implantation (23.5%), balloon angioplasty (5.9%), and cutting balloon angioplasty (5.9%). Stent fracture was seen in 6.7% of them. Procedural success was 100%. Angiographic follow-up data were available for 95 (91%) lesions. The rate of angiographic restenosis was 37.9%. In-stent late luminal loss of sirolimus-

Table 2 Baseline angiographic characteristics in in-stent restenosis lesions.

	$n = 105$ (%)
Treated coronary artery, *n*	
Left anterior descending	45 (42.9)
Right	35 (33.3)
Left circumflex	21 (20)
Left main tract	4 (3.8)
Morphologic pattern, *n*	
Focal (lesion length ≤10 mm)	80 (76.2)
Diffuse (lesion length >10 mm)	25 (23.8)
Total occlusion	13 (12.4)
Before intervention	
Reference vessel diameter, mm	2.78 ± 0.85
Minimum lumen diameter, mm	0.89 ± 0.79
%Diameter stenosis, %	69.4 ± 24.6
Lesion length, mm	9.8 ± 10.4
Type of drug-eluting stent, *n*	
Sirolimus-eluting stent	88 (83.8)
Paclitaxel-eluting stent	17 (16.2)
Stent length, mm	43 ± 27
Stent diameter, mm	3.1 ± 0.3
Maximal pressure, atm	18 ± 3
Prior bifurcation stenting with 2 drug-eluting stent, *n*	28 (26.7)
Stent fracture, *n*	7 (6.7)

Data are presented as number of patients and lesions (%) or mean ± SD.

Table 3 Procedural characteristics.

	$n = 105$ (%)
Type of intervention, *n*	
Sirolimus-eluting stent	42 (40.0)
Paclitaxel-eluting stent	24 (22.9)
Balloon angioplasty	23 (21.9)
Cutting balloon angioplasty	14 (13.3)
Bare-metal stent	2 (1.9)
Post intervention	
Minimum lumen diameter, mm	2.28 ± 0.87
Diameter stenosis, %	22.4 ± 15.8

Data are presented as number of patients and lesions (%) or mean ± SD.

Table 4 Multivariate analysis of risk for subsequent target lesion revascularization.

Variable	Univariate	Multivariate		
	p-Value	Odds ratio	95% CI	*p*-Value
Totally occluded ISR pattern	0.007	15.43	3.29—72.45	0.0005
Diabetes mellitus	0.01	3.45	1.20—9.93	0.02
Re-stenting with drug-eluting stent	0.0002	0.14	0.05—0.39	0.0002
Prior bifurcation stenting with 2 DES	0.03			

ISR, in-stent restenosis; DES, drug-eluting stent.

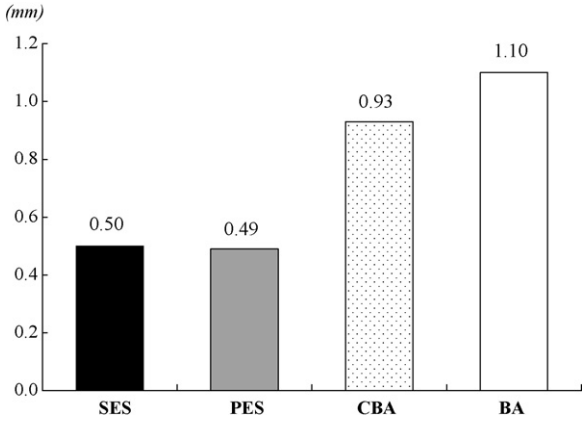

Figure 1 Late luminal loss in sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), cutting balloon angioplasty (CBA), and balloon angioplasty (BA) groups. Significantly lower lumen loss was observed in sirolimus-eluting stent and paclitaxel-eluting stent groups compared to balloon angioplasty group (0.50 ± 0.99 mm, 0.49 ± 1.00 mm, and 1.10 ± 0.68 mm, $p < 0.05$).

eluting stent, paclitaxel-eluting stent, cutting balloon, and balloon angioplasty were 0.50 ± 0.99 mm, 0.49 ± 1.00 mm, 0.93 ± 0.94 mm, and 1.10 ± 0.68 mm (Fig. 1). Re-stenting with DES (both sirolimus- and paclitaxel-eluting stents) was a lower late lumen loss than balloon angioplasty including cutting balloon: (0.51 ± 0.99 mm versus 1.02 ± 0.78 mm, $p = 0.02$). During the follow-up, TLR occurred in 35 patients (33.3%). Results of multivariate analysis are shown in Table 4. The following potential factors were entered into the model: age, female sex, diabetes, arterial hypertension, current smoking, hypercholesterolemia, hemodialysis, ejection fraction <40%, clinical presentation, prior bifurcation stenting with 2 DES, stent length, stent diameter, incidence of stent fracture, ISR after sirolimus-eluting stent, focal ISR pattern, diffuse ISR pattern, totally occluded ISR pattern, pre-vessel diameter, pre-MLD, pre % DS, lesion length, post-MLD, post % DS, maximum pressure, re-stenting with DES. The multivariate analysis revealed that totally occluded ISR (OR 15.43; 95% CI 3.29—72.45, $p = 0.0005$), and the presence of diabetes mellitus (OR 3.45; 95% CI 1.20—9.93, $p = 0.02$) were independent predictors of TLR. On the other hand, re-stenting with DES for DES-ISR was a protective factor (OR 0.14; 95% CI 0.05—0.39, $p = 0.0002$). Fig. 2 shows the rates of angiographic restenosis and TLR in 3 subsets according to the multivariate analysis.

Discussion

In the present study, we analyzed the predictors of subsequent TLR in a series of consecutive patients with DES-ISR undergoing PCI. Overall rates of angiographic and clinical restenosis were 37.9% and 33.3%, respectively, further suggesting that DES-ISR remains an unsolved problem. Our main results can be summarized as follows: in the era of DES, morphologic pattern of ISR plays a role for predicting recurrence of restenosis, and in particular, totally occluded ISR is associated with an increased risk. Furthermore, the presence of diabetes mellitus is also a strong independent predictor

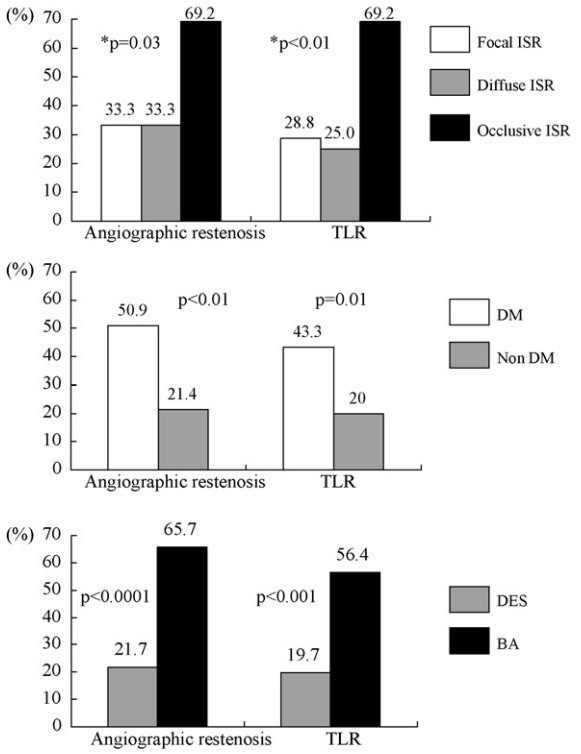

Figure 2 Angiographic restenosis and TLR in 3 subsets. (Upper) Morphologic ISR pattern, *p: focal versus totally occluded ISR. (Middle) DM versus non-DM. (Bottom) Re-stenting with DES versus balloon angioplasty (BA). TLR, target lesion revascularization; ISR, in-stent restenosis; DM, diabetes mellitus; DES, drug-eluting stent.

of TLR. In contrast, re-stenting with another DES plays a protective role against restenosis in patients with DES-ISR undergoing PCI.

In the era of BMS, morphologic pattern of ISR was the most important factor to predict recurrent restenosis after PCI for ISR. In particular, patients with diffuse ISR pattern were at high risk for recurrent restenosis after PCI. Previous studies demonstrated that 1-year TLR rate after PCI for BMS-ISR was 14—19% for focal ISR pattern, and 35—46% for diffuse ISR pattern [12,13]. On the other hand, the patients with DES-ISR appear to have different peculiarities when compared to those with BMS-ISR. The first, Colombo et al. showed in an early report, was that the ISR after DES implantation was of a focal pattern and mostly inside the stent [14]. Similar to that report, we also found the focal ISR pattern in 76.2% of patients. This morphologic change of DES-ISR seems to reflect the suppressive effect of in-stent neointimal hyperplasia by the DES. Unlike the focal ISR pattern of BMS, however, recurrence after treatment of the focal ISR pattern of DES was relatively high in the present study (33.3%). Furthermore, subsequent TLR after treatment of totally occluded ISR was at an unacceptably high rate (69.2%). These findings suggest that there may be different biological mechanisms for recurrence of DES-ISR. Although the exact mechanisms are not known, the differences in composition between DES and BMS might be able to account for mechanisms of DES-ISR. The DES is composed of anti-proliferative agents, and its carrier vehicle is

most frequently a polymer modifying drug-release kinetics. It is well known in some cases with DES implantation that non-absorbable polymer provokes chronic eosinophilic infiltration of the stented vessel, suggesting allergic reactions [15]. The polymer-induced inflammation may play a role in ongoing and aggressive neointimal proliferation which is in a total occlusive DES-ISR. Another possible explanation might be the presence of drug resistance to either sirolimus or paclitaxel. Theoretically, re-stenting with a different DES (so-called hetero" DES treatment) has the potential benefit of offering an alternative mechanism for preventing recurrent restenosis. However, a previous study has shown that a strategy of using a different DES-type to that originally implanted resulted in no differences between implantation of the same or a different DES in terms of preventing binary restenosis and major adverse cardiac events [10]. Incidentally, stent fracture may represent a new potential mechanism of restenosis after DES [16]. In our study, stent fracture was observed in 6.7% of DES-ISR, but it was not associated with an increased risk of recurrence after PCI in patients with DES-ISR.

Diabetes mellitus has traditionally been considered a major risk factor for the development of restenosis after PCI with or without BMS implantation [17]. In the era of DES, however, data from recent studies have not consistently related diabetes mellitus with increased rate of angiographic and clinical restenosis [18,19]. Interestingly, we found that the presence of diabetes mellitus was associated with recurrence after PCI for DES-ISR. There is a paucity of pathophysiology data in diabetic patients with DES-ISR, but Byrne et al. reported, with the results of 2-year re-angiographic data in 1331 patients, that the time course of restenosis in the DES era might be considered quite different. They found that ongoing late lumen loss beyond 6—8 months post-index procedure is observed in diabetic patients following DES implantation [20]. Several putative mechanisms, including more aggressive intimal hyperplasia, higher coagulability, a higher inflammatory response, and endothelial dysfunction, have been postulated to account for high recurrence after PCI in diabetic patients with DES-ISR [17]. We therefore think that not only waiting for the advance of DES technology, but also systemic approach to improve hyperglycemia, insulin resistance, and endothelial dysfunction are needed to reduce recurrence in patients with DES-ISR.

As already shown in the present study, the rates of angiographic restenosis and TLR were 37.9% and 33.3%, respectively. In this regard, a relatively higher rate of recurrence was observed than expected. Previous studies have reported that binary restenosis rate was found to be 16.7—26.4% [10,21]. This discrepancy can be explained by patient complexity of our study which had a high proportion of patients with diabetes mellitus and hemodialysis. An additional factor may have been the use of balloon angioplasty for treatment of DES-ISR. Indeed, the re-DES implantation among our patients with DES-ISR was protective and binary restenosis rate was 21.7%. Although a definitive conclusion cannot be drawn in terms of the best strategy for treatment of DES-ISR, at this moment it seems a reasonable therapeutic approach to use re-stenting with a second DES. On the other hand, concern has been raised that the stent sandwich strategy, putting two or three stent-strut one over another, may lead to an occurrence of stent thrombosis [22]. Therefore, we should be very careful in deciding on repeat revascularization for patients with DES-ISR. The patients with predictive factors, especially, may be needed to consider for the indication of coronary artery bypass graft surgery. Recently, a German group reported in patients with BMS-ISR, that paclitaxel-coated balloon was at least as efficacious and as well tolerated as the paclitaxel-eluting stent. Late lumen loss at 6 months was 0.38 mm in the paclitaxel-eluting stent versus 0.17 mm in the paclitaxel-coated balloon group, $p = 0.03$ [23]. Still, these data are from a small number of patients, but this strategy may be necessary to overcome some of these limitations. The present analyses should be interpreted with caution because of the non-randomized design and relatively small population. However our data are from multiple hospitals. Furthermore, we were also not able to make inferences about the relative efficacy of hetero DES treatment because stent selection was not made necessarily on the basis of any protocol.

In conclusion, we have demonstrated that the rates of angiographic restenosis and TLR are significant in this cohort of patients with DES-ISR. Angiographic pattern of DES-ISR and the presence of diabetes mellitus are the most important predictors of TLR, whereas re-stent implantation with a second DES is protective. These findings may facilitate improved outcomes after PCI in patients with DES-ISR. Prospective randomized trials to define the best treatment in DES-ISR subsets are warranted.

References

[1] Komatsu R, Ueda M, Naruko T, Kojima A, Becker AE. Neointimal tissue response at sites of coronary stenting in humans: macroscopic, histological, and immunohistochemical analyses. Circulation 1998;98:224—33.

[2] Eltchaninoff H, Koning R, Tron C, Gupta V, Cribier A. Balloon angioplasty for the treatment of coronary in-stent restenosis: immediate results and 6-month angiographic recurrent restenosis rate. J Am Coll Cardiol 1998;32:980—4.

[3] vom Dahl J, Dietz U, Haager PK, Silber S, Niccoli L, Buettner HJ, Schiele F, Thomas M, Commeau P, Ramsdale DR, Garcia E, Hamm CW, Hoffmann R, Reineke T, Klues HG. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). Circulation 2002;105:583—8.

[4] Iijima R, Ikari Y, Anzai H, Nishida T, Tsunoda T, Nakamura M, Hara K, Yamaguchi T. The impact of cutting balloon angioplasty for the treatment of diffuse in-stent restenosis. J Invasive Cardiol 2003;15:427—31.

[5] Stone GW, Ellis SG, O'Shaughnessy CD, Martin SL, Satler L, McGarry T, Turco MA, Kereiakes DJ, Kelley L, Popma JJ, Russell ME, TAXUS V ISR Investigators. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. JAMA 2006;295:1253—63.

[6] Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A, ISAR-DESIRE Study Investigators. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165—71.

[7] Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO,

Teirstein PS, Jaeger JL, Kuntz RE, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315—23.

[8] Mehilli J, Dibra A, Kastrati A, Pache J, Dirschinger J, Schömig A. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. Eur Heart J 2006;27:260—6.

[9] Qasim A, Cosgrave J, Latib A, Colombo A. Long-term follow-up of drug-eluting stents when inserted for on- and off-label indications. Am J Cardiol 2007;100:1619—24.

[10] Cosgrave J, Melzi G, Corbett S, Biondi-Zoccai GG, Babic R, Airoldi F, Chieffo A, Sangiorgi GM, Montorfano M, Michev I, Carlino M, Colombo A. Repeated drug-eluting stent implantation for drug-eluting stent restenosis: the same or a different stent. Am Heart J 2007;153:354—9.

[11] Kitahara H, Kobayashi Y, Takebayashi H, Fujimoto Y, Nakamura Y, Kuroda N, Himi T, Miyazaki A, Haruta S, Komuro I. Re-restenosis and target lesion revascularization after treatment of sirolimus-eluting stent restenosis: retrospective analysis of 4 Japanese hospitals. Circ J 2009;73:867—71.

[12] Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872—8.

[13] Nobuyoshi M, Yokoi H. How to manage in-stent restenosis. Catheter Cardiovasc Interv 2000;49:30—1.

[14] Colombo A, Orlic D, Stankovic G, Corvaja N, Spanos V, Montorfano M, Liistro F, Carlino M, Airoldi F, Chieffo A, Di Mario C. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. Circulation 2003;107:2178—80.

[15] Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701—5.

[16] Aoki J, Nakazawa G, Tanabe K, Hoye A, Yamamoto H, Nakayama T, Onuma Y, Higashikuni Y, Otsuki S, Yagishita A, Yachi S, Nakajima H, Hara K. Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. Catheter Cardiovasc Interv 2007;69:380—6.

[17] Smith Jr SC, Faxon D, Cascio W, Schaff H, Gardner T, Jacobs A, Nissen S, Stouffer R. Prevention conference VI: diabetes and cardiovascular disease: writing group VI: revascularization in diabetic patients. Circulation 2002;105:165—9.

[18] Iijima R, Ndrepepa G, Mehilli J, Markwardt C, Bruskina O, Pache J, Ibrahim M, Schömig A, Kastrati A. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. Am Heart J 2007;154:688—93.

[19] Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, Dirschinger J, Schömig A. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293—300.

[20] Byrne RA, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schömig A, Kastrati A. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. JACC Cardiovasc Interv 2009;2:291—9.

[21] Byrne R, Iijima R, Mehilli J, Pache J, Schulz S, Schömig A, Kastrati A. Treatment of paclitaxel-eluting stent restenosis with sirolimus-eluting stent implantation: angiographic and clinical outcomes. Rev Esp Cardiol 2008;61:1134—9.

[22] Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005;112:270—8.

[23] Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986—94.